

## REMARKS

### Newly Presented Claims

Applicants note that new dependent claims 32 to 42 have been added by this amendment. The new claims are directed to particular species of the claimed anti-CD20 antibody that is the subject of the presented method claims. Support for the claims may be found, *inter alia*, at the following locations of the specification: page 2, lines 21 to 25 (“rituximab”); page 13, lines 25 to page 14 (“chimeric antibodies”), line 6; page 14, line 7 to line 22 (“humanized antibodies”); and page 15, line 8 to line 24 (“rituximab”, “Y2B8”, “<sup>131</sup>I-B1”).

### Statement of the Substance of the Interview

During the interview conducted with Examiner Chan and Examiner Haddad on May 6, 2004, Applicants’ representatives discussed the rejections set forth in the Office Action mailed on January 16, 2004. Applicants indicated that they would provide publications directed to clinical investigations of the use of anti-CD20 antibodies in different types of graft settings to address and resolve rejections based on 35 U.S.C. § 112, first paragraph. The Examiners agreed to consider the publications, and indicated that, if the publications demonstrated utility across the claimed genus, the submission would address the questions that were the basis of the rejections under 35 U.S.C. § 112, first paragraph.

Applicants accordingly submit herewith an Information Disclosure Statement (IDS) that includes post-filing publications that show the use of rituximab in allogeneic graft settings. The publications illustrate positive clinical investigations of rituximab in a variety of graft settings including, *inter alia*, heart transplantation (*Aranda et al.*, TRANSPLANTATION,

73(6):907-910 (March 27, 2002) and *Garrett et al.*, ANN. THORAC. SURG. 74:1240-2 (2002)); simultaneous pancreas-kidney transplantation and renal allograft (*Becker et al.*, TRANSPLANTATION, 69(8)(supplement):S362 (Abstract #964)(April 27, 2000)); kidney transplantation (*Sawada et al.*, TRANSPLANTATION, 74(9):1207-1210 (November 15, 2002)); ABO-incompatible kidney transplantation (*Tyden et al.*, TRANSPLANTATION, 76(4):730-743 (August 27, 2003)); lung allograft (*Pierson et al.*, TRANSPLANTATION, 74(1): 79-84 (July 15, 2002)); and simultaneous pancreas-kidney transplantation (*Sammartino et al.*, AM. J. TRANSPLANTATION, 4:140-143 (2004)). Each of these documents was published after the filing date of the present application, and none are prior art to the invention defined in the presented claims. The Examiner is invited to consider these publications, as well as the other publications cited on the enclosed IDS.

During the interview, certain potential amendments to the claims were discussed. In particular, Applicants proposed to amend claim 1 to recite that the graft is an “allogeneic” graft, proposed amending claim 28 to indicate that the graft is an isograft and that the method is practiced on a human, and proposed amending claim 13 to recite administering a dose of from “about 20 mg/m<sup>2</sup> to about 1000 mg/m<sup>2</sup>”. Applicants consequently have amended claim 1 to recite that the graft is an allogeneic graft (see, e.g., page 7, lines 7 to 10). Applicants also have amended claim 13 to specify that the dose is from “about 20 mg/m<sup>2</sup> to about 1000 mg/m<sup>2</sup>” (see, e.g., page 41, lines 25 to 27)

With regard to the proposed amendment to claim 28 concerning the term “isograft”, Applicants note that, as indicated in the interview and as set forth in the specification (see, e.g., page 7, lines 11 to 12), the term “isograft” refers to the situation where the donor of the graft is a human of the same or different genetic origin as the recipient of the graft. For purposes of clarity, claim 28 has been amended to specify that the graft is from a donor

human of the same or different genetic origin as the human being treated according to the claimed method, as discussed.

Also during the interview, the Examiners requested information from Applicants concerning the public availability of certain antibodies that are identified in the patent specification and the claims. In particular, the Examiners requested information concerning the public availability of antibodies designated in the specification as “Y2B8” and “<sup>131</sup>I-B1.” As set forth in the specification at page 15, line 10, the term “Y2B8” refers to a Y<sup>90</sup> radiolabeled 2B8 antibody. The “2B8” antibody is a murine antibody produced by a hybridoma that was deposited under the Budapest treaty on June 22, 1993 with the American Type Culture Collection under deposit number HB11388. The 2B8 antibody is described at column 32, lines 1 to 9 of U.S. Patent No. 5,736,137, which is expressly incorporated by reference into the present specification. The “Y2B8” antibody, per the specification, is a <sup>90</sup>Y-labeled version of the 2B8 antibody. Antibody “<sup>131</sup>I-B1” is disclosed in the specification at page 15, line 12. This antibody, as set forth therein, is a <sup>131</sup>I-labeled version of the B1 antibody, which is a commercially available murine antibody under the tradename BEXXAR, from the Corixa Corporation. The generic name of “I<sup>131</sup>-B1” or BEXXAR is “Iodine I131 Tositumomab.” The B1 (Tositumomab) antibody is disclosed at column 7, lines 36-37 of USP 5,595,721, which is expressly incorporated by reference into the present specification. Applicants note that the use of these terms in the specification is in a manner that unambiguously identifies the specific antibody in question. In view of this, and of the fact of the publicly availability of the antibodies and their sources, Applicants submit that no claim amendments are necessary.

Inventorship Issues

Applicants wish to bring to the attention of the Office information regarding the designated inventorship of the present application. Specifically, Applicants herewith provide the Office with a copy of a report concerning the inventorship of certain claims that are either now pending or have been canceled from the present application. Applicant notes that the basis of the report was PCT application no. WO 01/03,734 (previously provided to the Office on , which claims priority as the present application does, to provisional application 60/144,405. The PCT application has the same disclosure as the present application.

According to the report, the presently named inventors are the correct inventive entity of claims 1 to 27 and 29 to 31 in the published PCT application. The report also indicates that Dr. Mark Pescovitz was the sole inventor of claim 28 of the published PCT application, a claim that is not pending in this application. Based on these observations, no change is required to the inventive entity of the present application. A copy of the report is provided in the enclosed IDS.

35 U.S.C. §112 Rejection of Claim 13

In the Office Action dated January 16, 2004, the Examiner rejected claim 13 under 35 U.S.C. §112, first paragraph, as containing subject matter which the Examiner believes was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Without acquiescing to the merits of the above-noted rejection, Applicants have elected to amend claim 13 to recite a dosage range of “from about 20 mg/m<sup>2</sup> to about 1000

mg/m<sup>2</sup>". The dosage range is supported by the disclosure at page 41, lines 26-27 of the specification and specifically encompasses dosages above, at, or below 375 mg/m<sup>2</sup>, as well as other dosages within this range.

The Examiner is respectfully requested to withdraw the rejection of claim 13 under 35 U.S.C. §112, first paragraph (written description) in view of the above.

35 U.S.C. §112 Rejection of Claims 1, 5-16, 22 and 28

In paragraph 7 of the Office Action dated January 16, 2004, the Examiner rejected claims 1, 5-16, 22 and 28 under 35 U.S.C. §112, first paragraph, as not being enabled by the disclosure.

At pages 3 and 4 of the last Office Action, the Examiner recites a variety of theories that suggest that he has certain questions regarding the operability of the claimed invention. For example, the Examiner raises questions regarding whether anti-CD20 antibodies would block/treat any type of foreign graft in a mammal including GVHD or HVGD, and that certain issues may exist with regard to the role played by humoral and/or T cell-mediated immune responses against grafts. The Examiner cites *Krenger and Ferrara*, IMMUNOLOGY RES. 15:50-73 (1996) and *Aranda et al.*, TRANSPLANTATION, 73:6, 907-910 (2002), in this regard. The Examiner also cites *Alwayn et al.*, (XENOTRANSPLANTATION, 8:157-171, 2001) for the suggestion that "antialphaGal Abs could be "a major barrier to clinical xenotransplantation as they are believed to initiate both hyperacute and acute humoral rejection." The Examiner also notes that "one skilled in the art at the time the invention was made would doubt that the B-cells are associated with the graft destruction to be useful as a therapeutic target." The Examiner also raises questions with regard to the long-term viability of using of anti-CD20 antibodies in graft settings, and whether there are species- or model-

dependent issues involved in treatment of graft rejections. These and other observations are set forth in paragraph 7, at pages 3 and 4 of the last Office Action.

Applicants have fully considered the rejection under 35 U.S.C. § 112, first paragraph, as set forth in the last Office Action. Applicants herewith provide copies of published reports of successful clinical evaluation of an anti-CD20 antibody, rituximab, to block an immune response to a graft in a mammal. The clinical investigations establish that rituximab has been used successfully in variety of graft scenarios, as discussed above. Applicants note that the Examiner had indicated in the interview of May 6, 2004, that such evidence of successful treatment in a variety of graft settings would be relevant to overcoming the basis for this enablement rejection. Applicants invite the Examiner to fully review and consider this evidence, which Applicants submit address the concerns expressed in the last Office Action as to whether the claimed methods are operative.

Applicants also submit that the theories recited by the Examiner in the rejection under §112, first paragraph, are rendered moot by the provision of the above-identified publications showing successful clinical evaluations using an anti-CD20 antibody in a variety of graft scenarios. In view of the above arguments and publications, Applicants believe that the rejections based on lack of enablement have been fully addressed. Applicants accordingly request the Examiner to withdraw the rejections based on 35 U.S.C. §112, first paragraph.

**CONCLUSION**

In light of the above amendments and remarks, Applicants respectfully submit that all pending claims as currently presented are in condition for allowance. If, for any reason, the Examiner disagrees, please call the undersigned attorney at 202-736-8914 so that Applicants may attempt to resolve any matter still outstanding *before* issuing another action. Favorable reconsideration is respectfully requested.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'JP Kushan', with a long horizontal flourish extending to the right.

Jeffrey P. Kushan  
Registration No. 43,401  
Attorney for Applicants

SIDLEY AUSTIN BROWN & WOOD LLP

1501 K Street, N.W.  
Washington, D.C. 20005  
Phone: 202-736-8914  
Fax: 202-736-8711

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